Vasculitis

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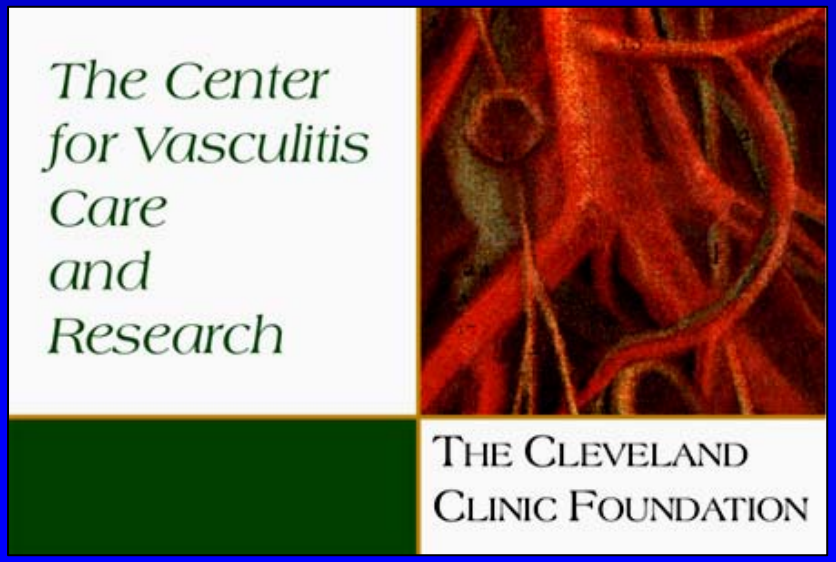

CME Disclosure Statements

Carol A. Langford, MD, MHS

Employment

- None

Financial Interests

- None

Research Interests

- Study drug provided by: Genentech, Bristol-Myers Squibb

Organizational Interests

- None

Gifts

- None

Other Interests

- None

CME Disclosure Statements

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Unlabeled use of commercial products

To date, there are no therapeutic agents specifically approved for the treatment of vasculitis

All references to use of a commercial product discussed in this presentation constitute an unlabeled use of the product

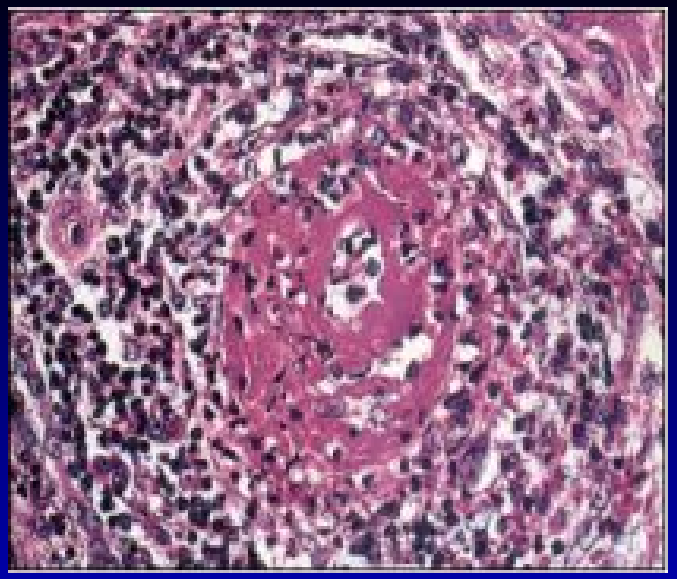
Vasculitis

Why is vasculitis important to the allergist/immunologist ?

- Vasculitis is an immunologically mediated process
- Undiagnosed vasculitic disease may be referred for allergy consultation

  (sinus disease and asthma are seen in certain forms of vasculitis)
- In some communities, vasculitis patients managed by allergists
- Included in Board examinations

Vasculitis = Inflammation of the Blood Vessel



inflammation

↓

blood vessel damage

↙ ↘

compromise of vessel lumen → organ ischemia

attenuation of vessel wall → aneurysm formation hemorrhage

Presenting Features of Vasculitis

Systemic symptoms:

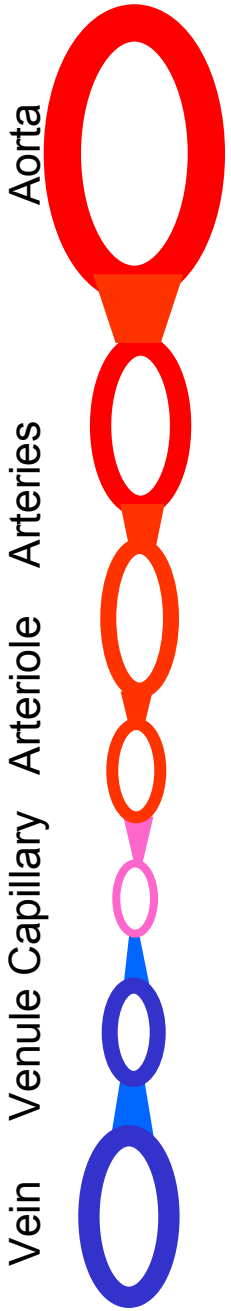
As evidenced by histology: vasculitis is an inflammatory process

fever, night sweats
fatigue, malaise
anorexia, weight loss
arthralgias, myalgias

Organ specific symptoms / signs of tissue injury

Influenced by:

degree of collateral circulation
underlying health of organ
the size of blood vessel that is affected



	Example	Clinical Consequence
Large Vessel		
	Aorta	stenosis, aneurysm
	Subclavian artery	arm claudication
	Ophthalmic artery	blindness
Medium Vessel		
	Digital artery	blue ischemic digit
	Mesenteric artery	bowel infarction
	Epineural arteries	mononeuritis (foot drop)
Small Vessel		
	Skin	palpable purpura
	Kidney	glomerulonephritis
	Lung	pulmonary hemorrhage

Wide range of severity
Wide range of presentations

Vasculitis is not one specific disease

Blood vessel inflammation can be seen in a variety of settings

Primary Vasculitides

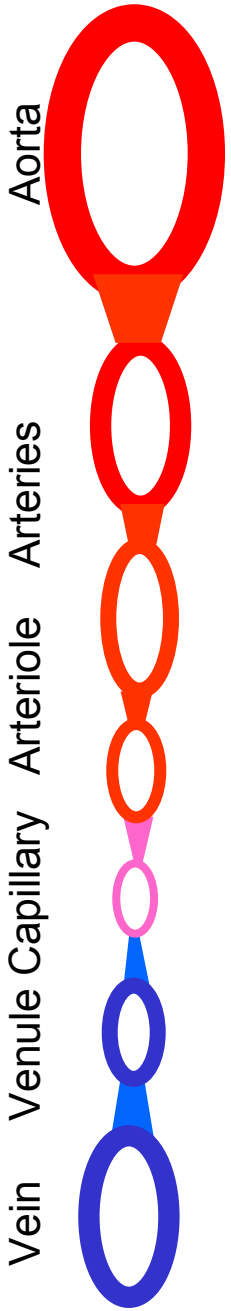
Unique disease entities without a currently identified underlying cause where vasculitis forms the pathological basis of tissue injury

- Takayasu's arteritis
- Giant cell arteritis
- Kawasaki disease
- Polyarteritis nodosa
- Wegener's granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome
- Henoch-Schönlein purpura

Secondary Vasculitides

Vasculitis occurring secondary to an underlying disease or exposure

- Medications
- Infection
- Malignancy
- Transplant
- Connective tissue disease
- Cryoglobulinemia



Large Vessel

Takayasu's arteritis
Giant cell arteritis

Medium Vessel

Kawasaki disease
Polyarteritis nodosa

Small Vessel

Wegener's granulomatosis
Microscopic polyangiitis
Churg-Strauss syndrome

Henoch-Schönlein purpura
Cryoglobulinemic vasculitis

Cutaneous leukocytoclastic vasculitis

How Do Forms of Primary Vasculitis Differ ?

Vessel size:	large, medium, small vessel
Epidemiology:	age, sex, ethnicity, frequency
Clinical Manifestations:	symptoms, signs patterns of organ involvement
Diagnosis:	biopsy arteriography clinical features + laboratory abnormalities
Treatment and Outcome:	prednisone cytotoxic therapy (cyclophosphamide) supportive care other therapies

Giant Cell Arteritis

(Also called temporal arteritis)

Epidemiology

Granulomatous large vessel vasculitis

Preferentially affects the extracranial branches of the carotid artery

The most common form of systemic vasculitis

Occurs over the age of 50

2:1 Female:Male

Giant Cell Arteritis

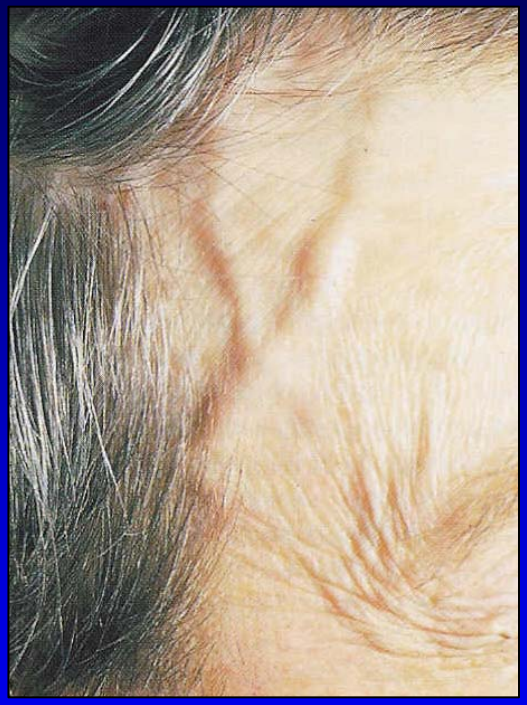
Clinical Manifestations

Symptoms:

- Fever
- Fatigue
- Headache
- Scalp tenderness
- Jaw / tongue claudication
- Polymyalgia rheumatica (40-50%)
  (pain along hip and shoulder girdle)

Signs

Nodular, tender temporal artery
with diminished or absent pulsation



From: Klippel and Dieppe. Rheumatology

Most dreaded complication:

Visual loss due to optic nerve ischemia from arteritis of ocular vessels

Giant Cell Arteritis

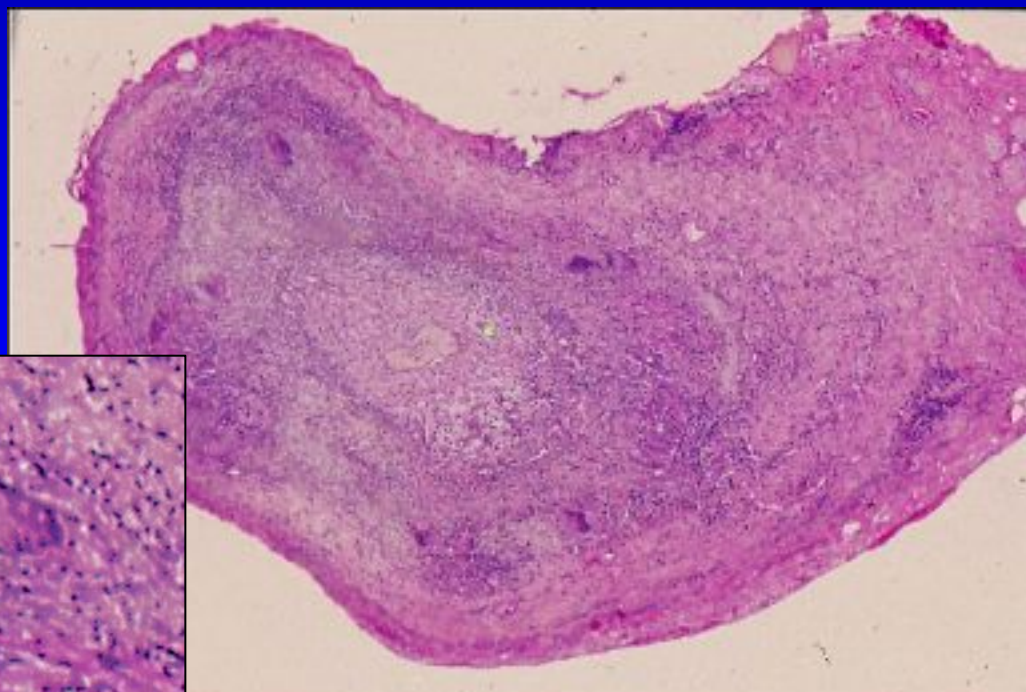
Diagnosis

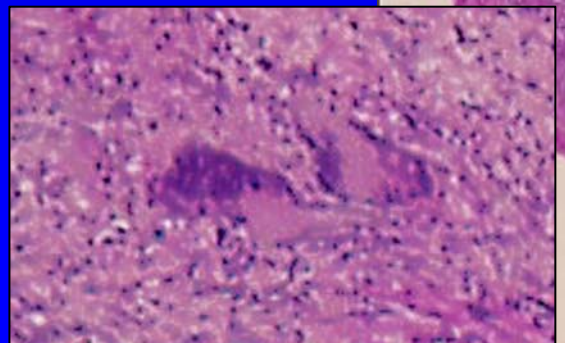
Suggested by:

- Compatible age, symptoms, signs
- Elevated erythrocyte sedimentation rate (ESR)

Diagnosed by: temporal artery biopsy

- Panmural mononuclear infiltration
- Disruption internal elastic lamina
- Giant cells





Giant Cell Arteritis

Treatment Outcome

Prednisone 40-60mg daily

- Reduces symptoms and prevents visual loss
- Begin immediately while biopsy is being arranged
- Most patients require treatment for > 2 years

Aspirin 81mg daily

- Found to reduce cranial ischemic complications
- Should be given in all patietns without contraindications

Cytotoxic agents

- Not standardly given
- Methotrexate – studied in 2 randomized trials with divergent results

- Acute mortality very uncommon
  - May be late mortality from thoracic aortic aneurysms
- Relapse requiring an increase in steroid dose occurs in 26-90%

Kawasaki Disease

Epidemiology

Vasculitis of large, medium, and small arteries

Disease of children – 80% occur prior to age 5 years

Primary cause of acquired heart disease
(from coronary arteritis)
in children from the USA and Japan

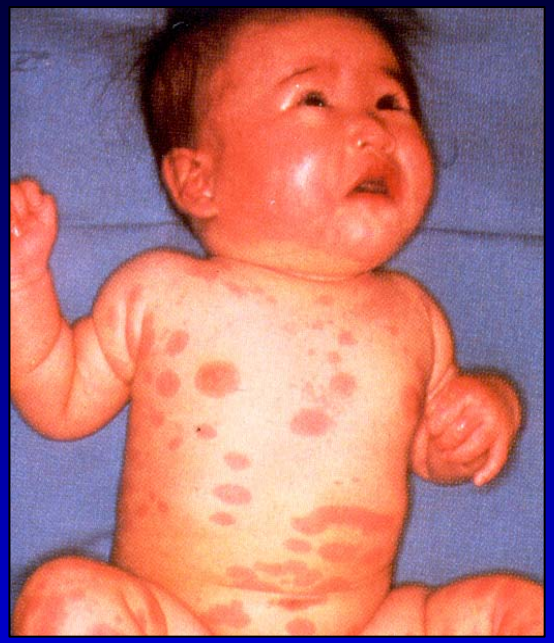
Kawasaki Disease

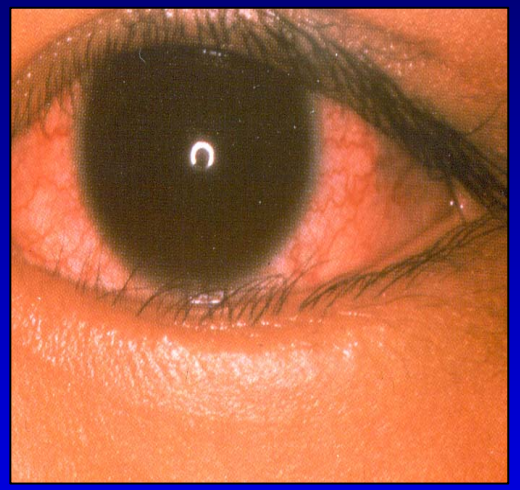
Clinical Manifestations

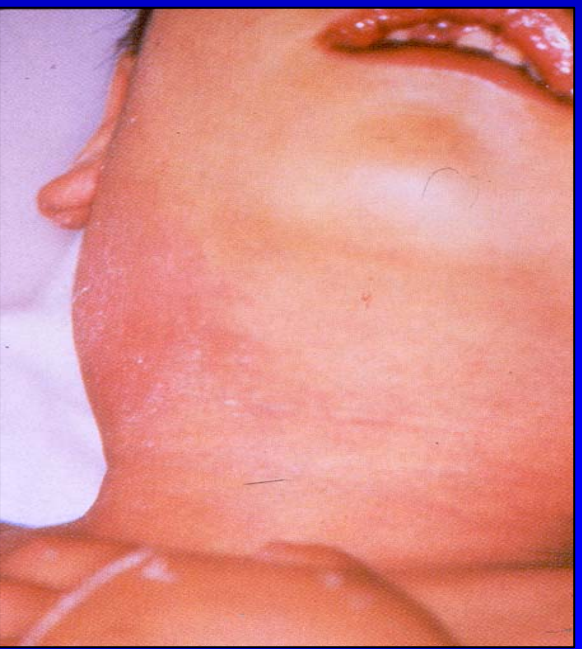
Acute febrile illness

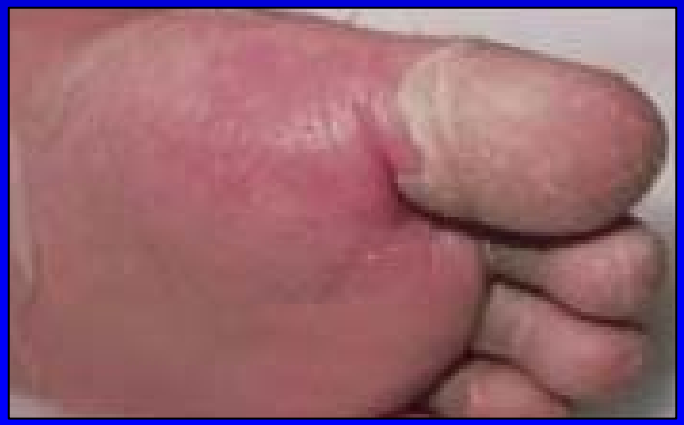
Followed within 1-3 days by:

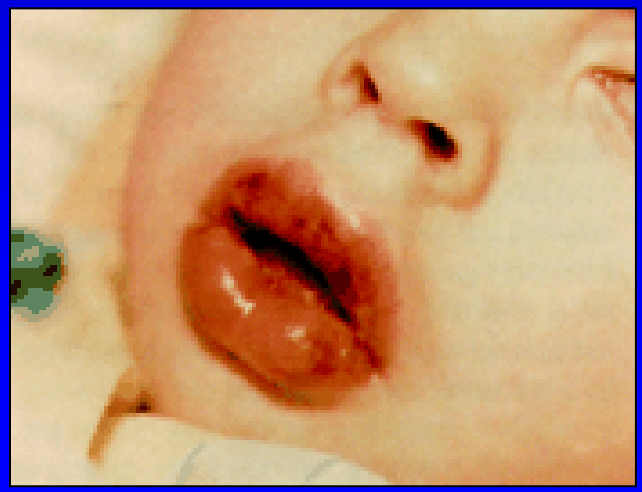
- rash
- conjunctival injection
- cervical adenopathy
- extremity changes
- oral mucosal changes











Courtesy of Karyl Barron MD

Kawasaki Disease

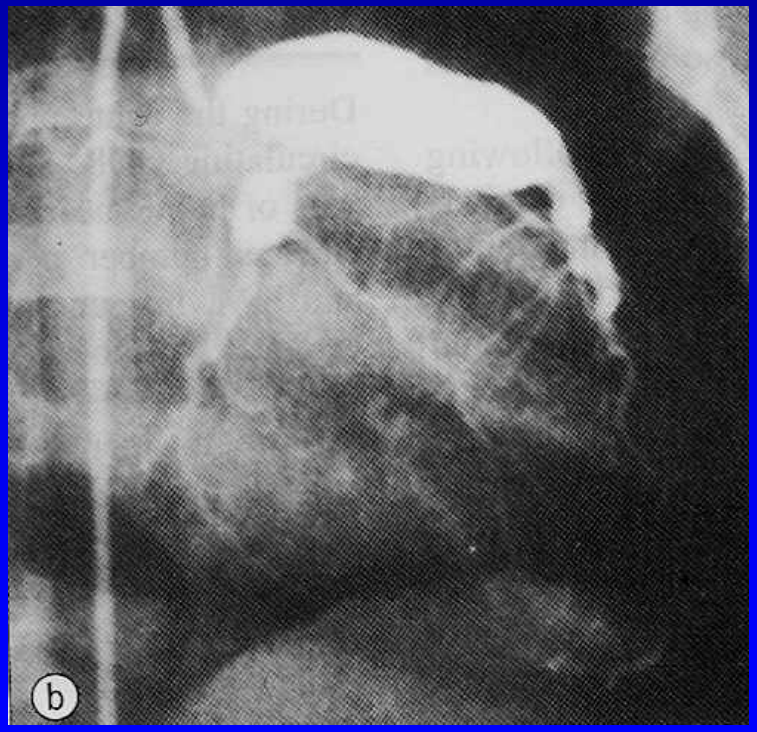
Clinical Manifestations

Primary complication

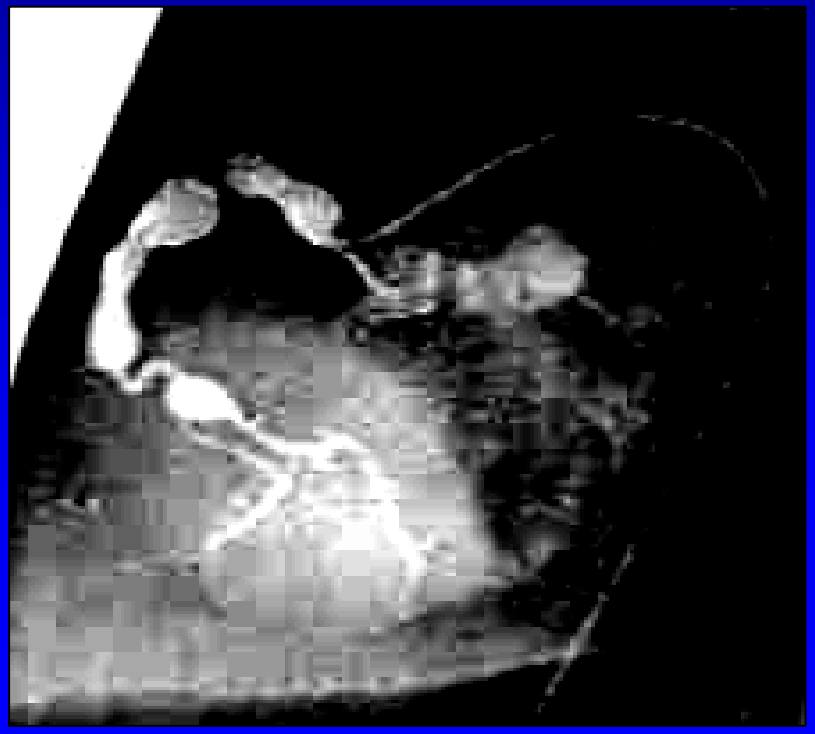
- Coronary artery aneurysms

appear 1-4 weeks after fever onset

develop in 15-25% of untreated patients



From: Klippel and Dieppe. Rheumatology



Courtesy of Karyl Barron MD

Kawasaki Disease

Diagnosis

Diagnosis is clinical

Based on
Fever + 5 features

- rash
- conjunctival injection
- cervical adenopathy
- extremity changes
- oral mucosal changes

Kawasaki Disease

Treatment Outcome

Intravenous immunoglobulin (IVIg)

2 g/kg as a single dose - reduces risk of aneurysms

Aspirin – given concurrently

- 1-2% acute mortality – risk is of late mortality from aneurysms
- Relapses are uncommon (3-5%)

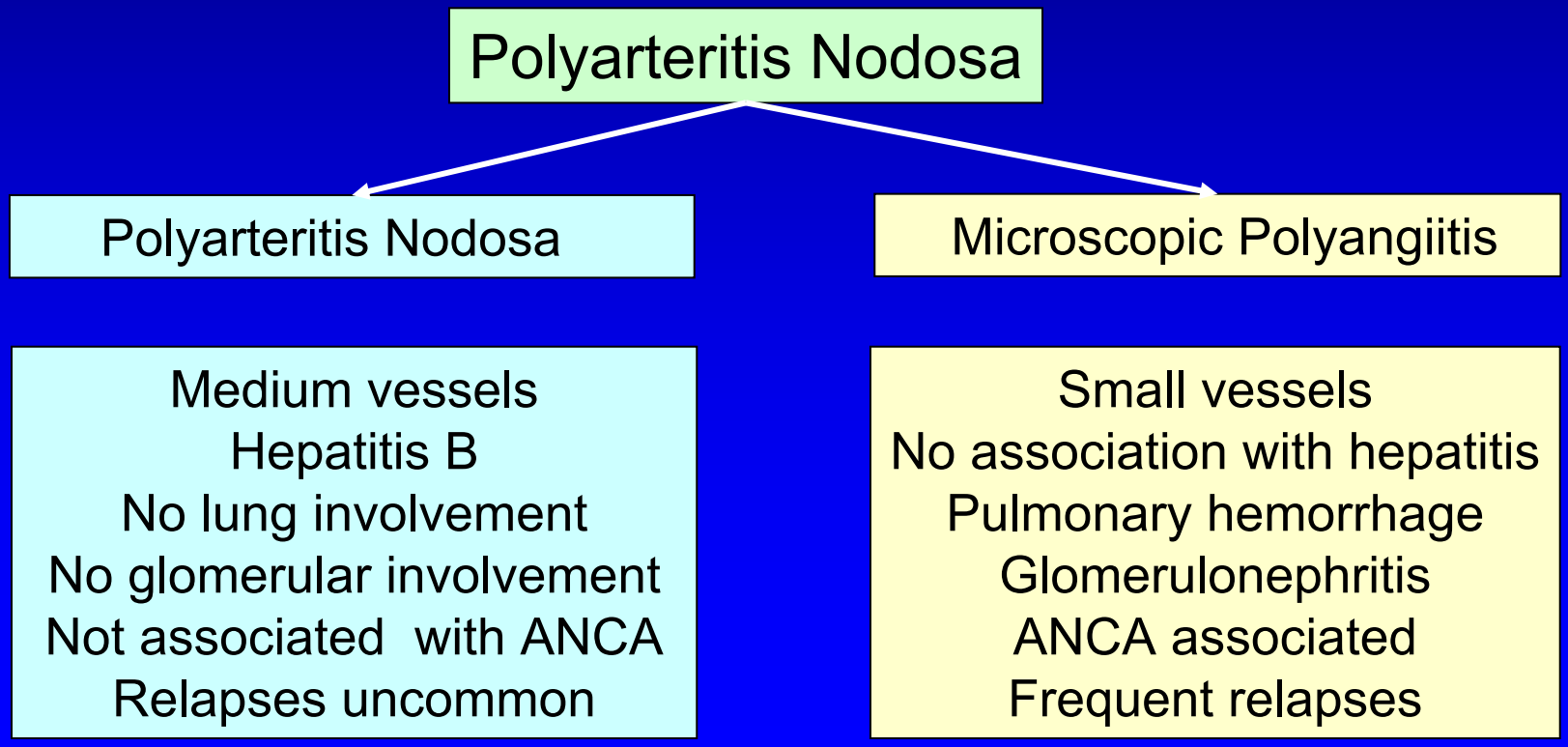
Polyarteritis Nodosa

Epidemiology

First form of vasculitis described

Has since gone through changes in nomenclature

1994 – Chapel Hill Consensus Conference

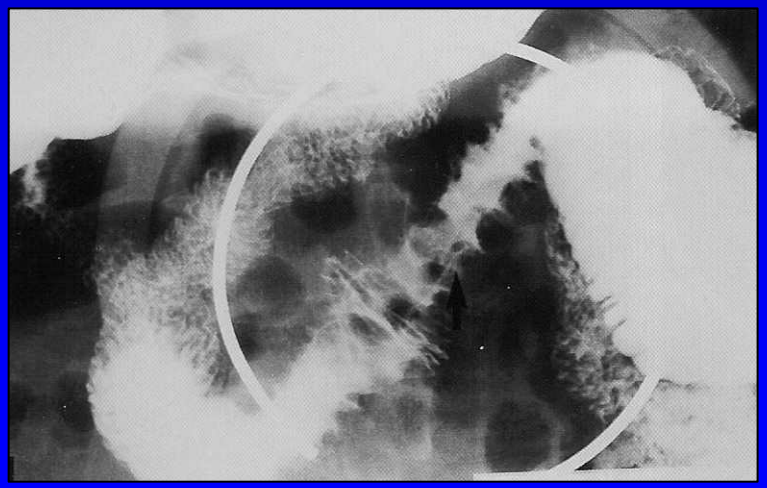


Polyarteritis Nodosa

Clinical Manifestations

Often presents acutely

Constitutional features	fever, weight loss, arthralgias, night sweats
Nerve	mononeuritis multiplex (ie: foot drop, wrist drop) CNS disease
Renal	hypertension, infarction (not a glomerulonephritis)
Gastrointestinal tract	pain, infarction, perforation, bleeding
Heart	
Digital infarction	



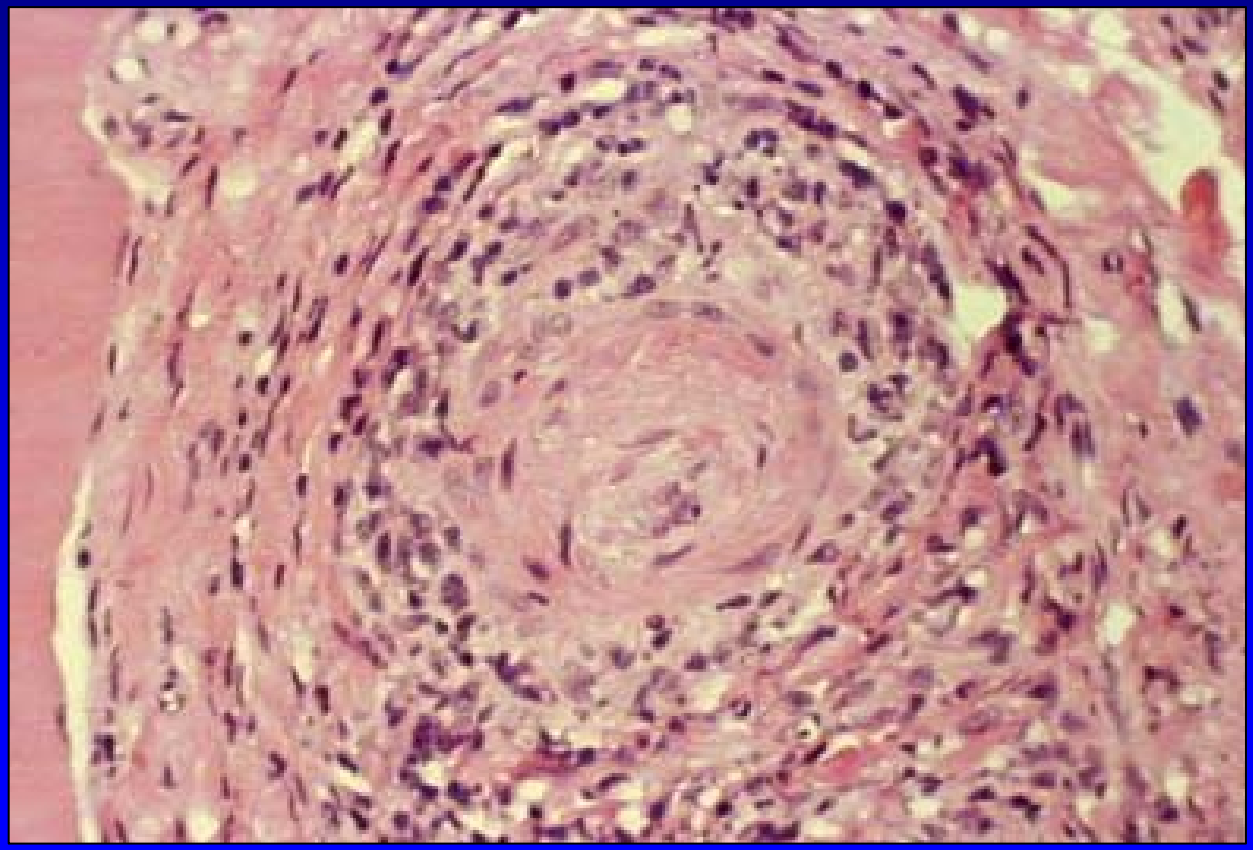
From: Keeffe. Atlas of Gastroenterology

Polyarteritis Nodosa

Diagnosis

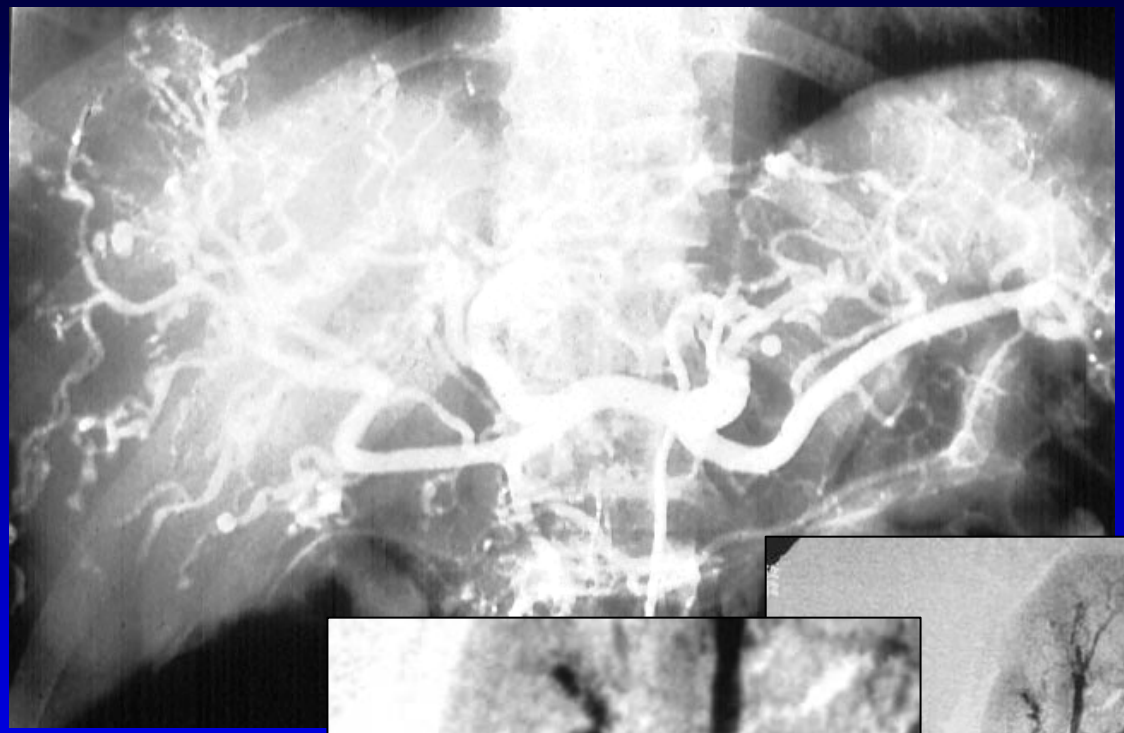
Biopsy

Necrotizing inflammation of medium or small arteries
With abundant neutrophils and fibrinoid changes

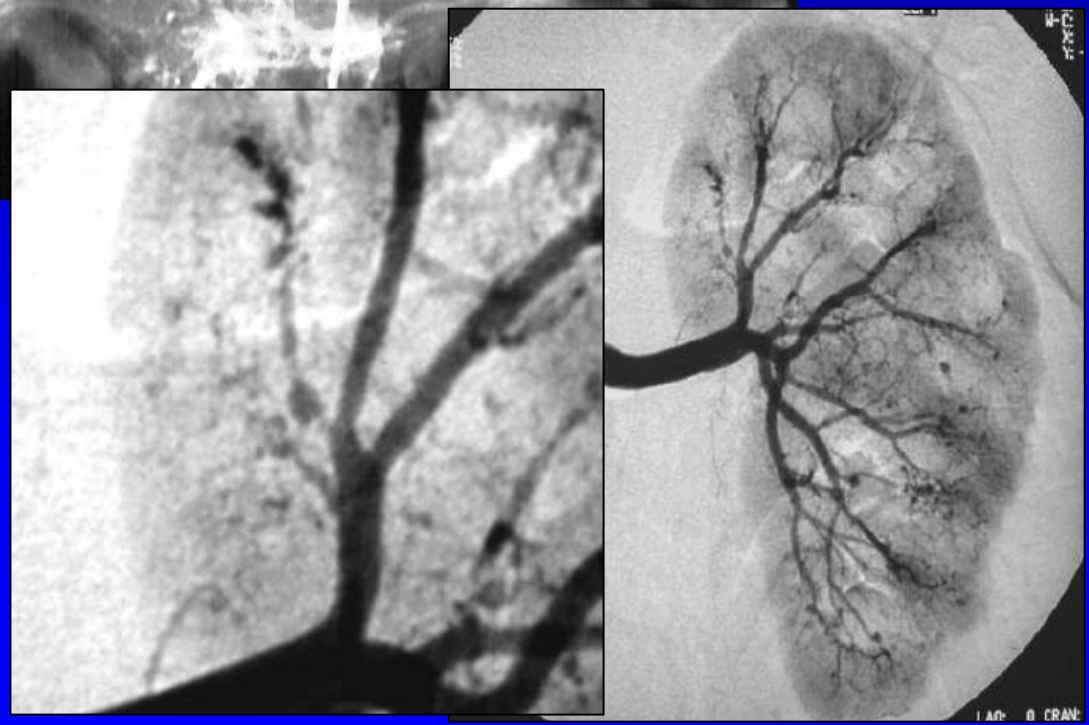


Polyarteritis Nodosa

Diagnosis



Arteriogram



Visceral and renal circulation

stenoses, beading
microaneurysms

Polyarteritis Nodosa

Treatment Outcome

PAN - Hepatitis B Associated

anti-viral therapy plays an important role
immunosuppressive therapy only as necessary to control vasculitis

PAN - Non-Hepatitis Associated

Based on severity

Prednisone + daily cyclophosphamide for life-threatening disease
Prednisone alone may be considered for non-severe disease

- 80% estimated 5 year survival with treatment
- Relapses occur in < 10%

Daily Cyclophosphamide

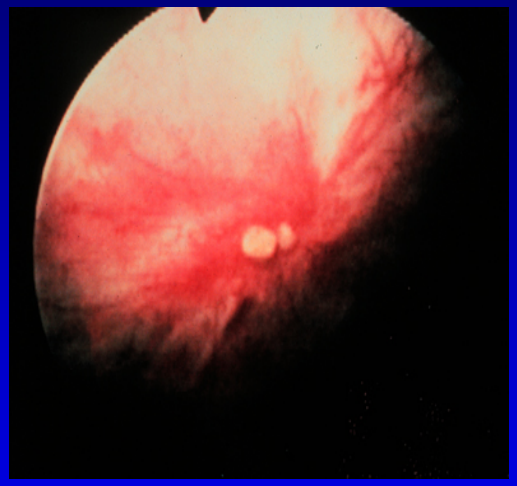
A life saving drug in severe systemic vasculitis – but toxic

Acute toxicities

- Infection
- Cytopenias
- Bladder injury

Long Term Toxicities

- Infertility
- Malignancies
  - Bladder
  - Blood (leukemia, lymphoma)
  - Skin (basal and squamous cell)



Toxicity prevention:

- Take in the AM with a large amount of fluid
- CBC every 1-2 weeks while on drug
- Urinalysis with cystoscopy for non-glomerular hematuria
- Urine cytology every 6 months

Cancer risk and need for surveillance is life long

Wegener's Granulomatosis

Epidemiology

Vasculitis affecting the small to medium vessels
Granulomatous inflammation of the respiratory tract

Adults age 40-60 years
can be seen in all ages

Women = Men

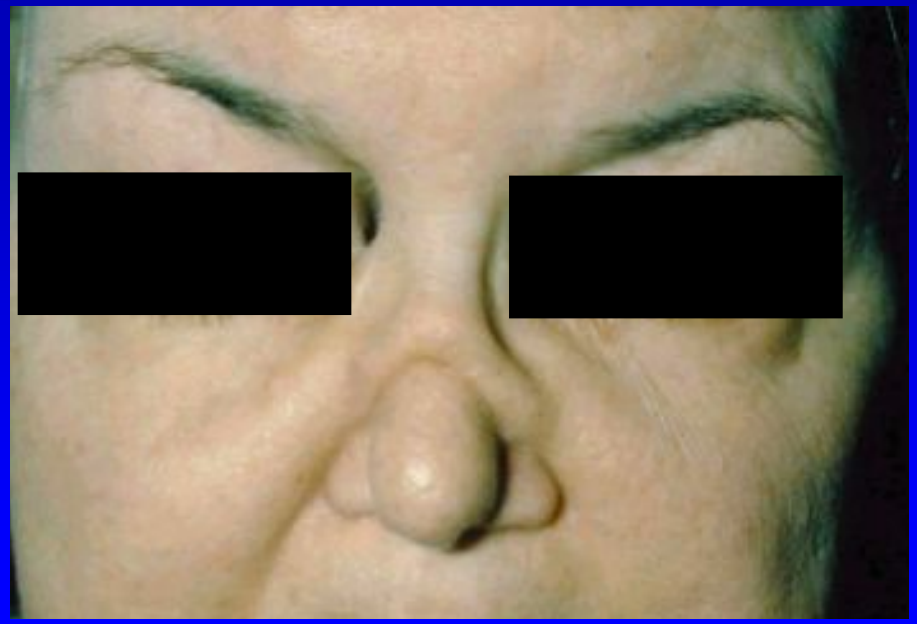
Uncommon – affects 3 in 100,000

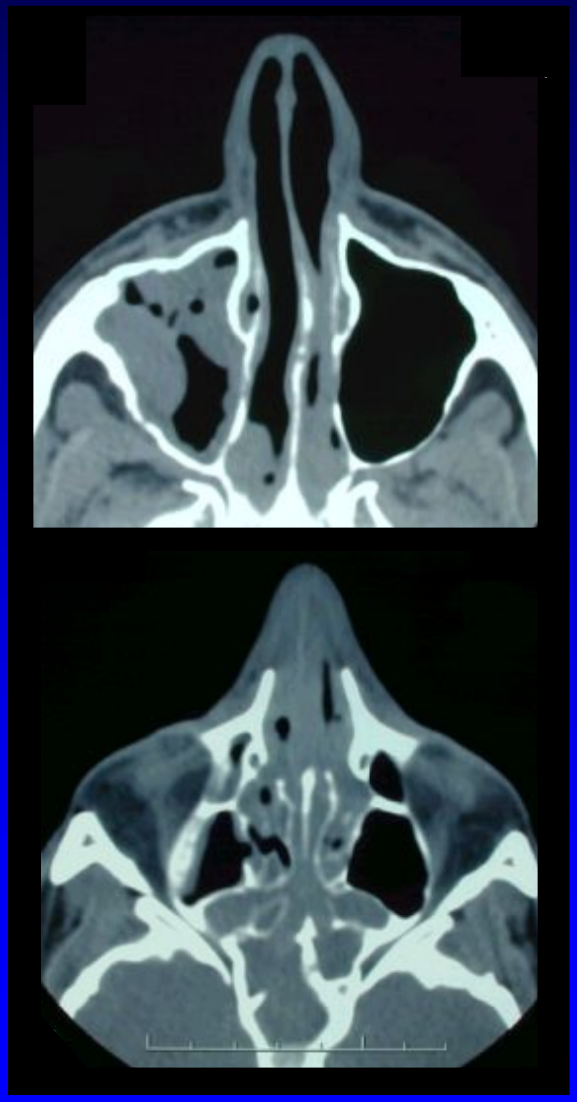
Wegener's Granulomatosis

Clinical Manifestations

Sinus

affected in 95% of patients



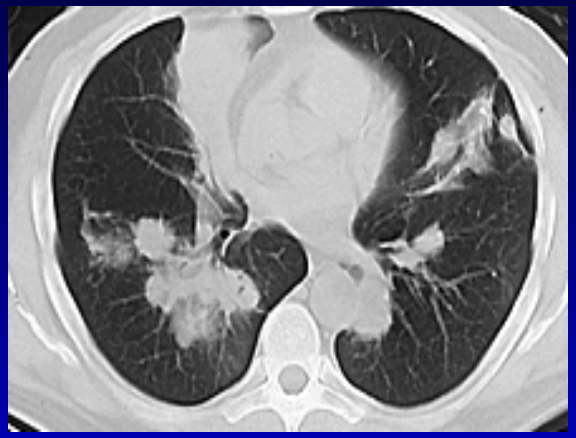


Wegener's Granulomatosis

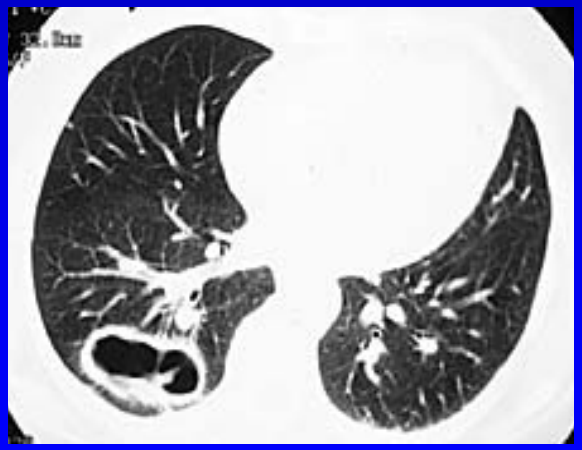
Clinical Manifestations

Lung

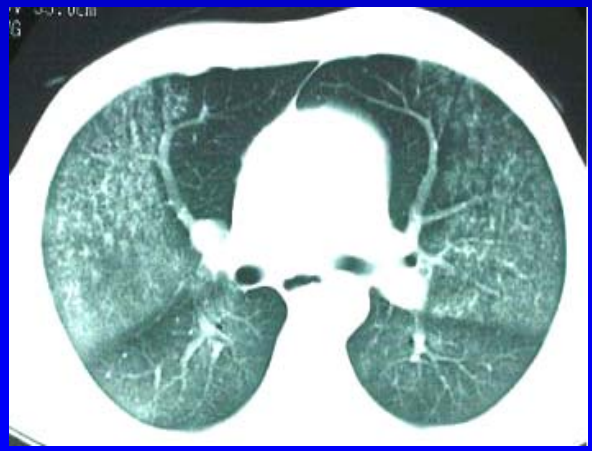
affected in 85%



Pulmonary nodules
infiltrates



Cavitary lesions



Pulmonary hemorrhage

Wegener's Granulomatosis

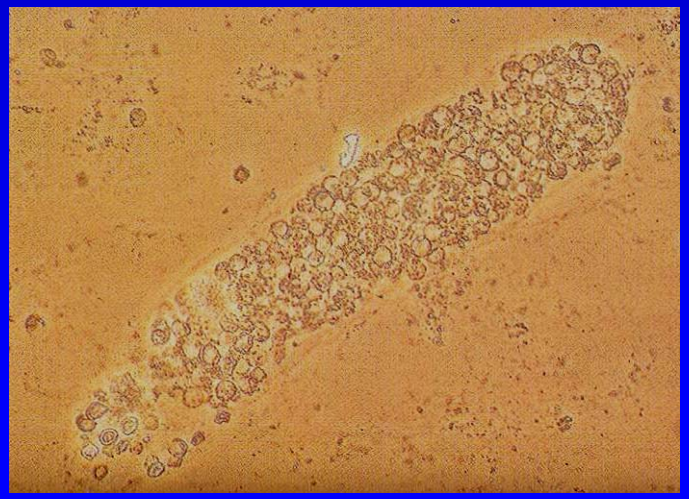
Clinical Manifestations

Kidney - 80% affected during disease course
20% have glomerulonephritis at diagnosis

typically asymptomatic
can be rapidly progressive
may lead to renal failure

Detected by urinalysis:

Proteinuria
Hematuria
Red blood cell casts



Wegener's Granulomatosis

Clinical Manifestations

Organ triad:

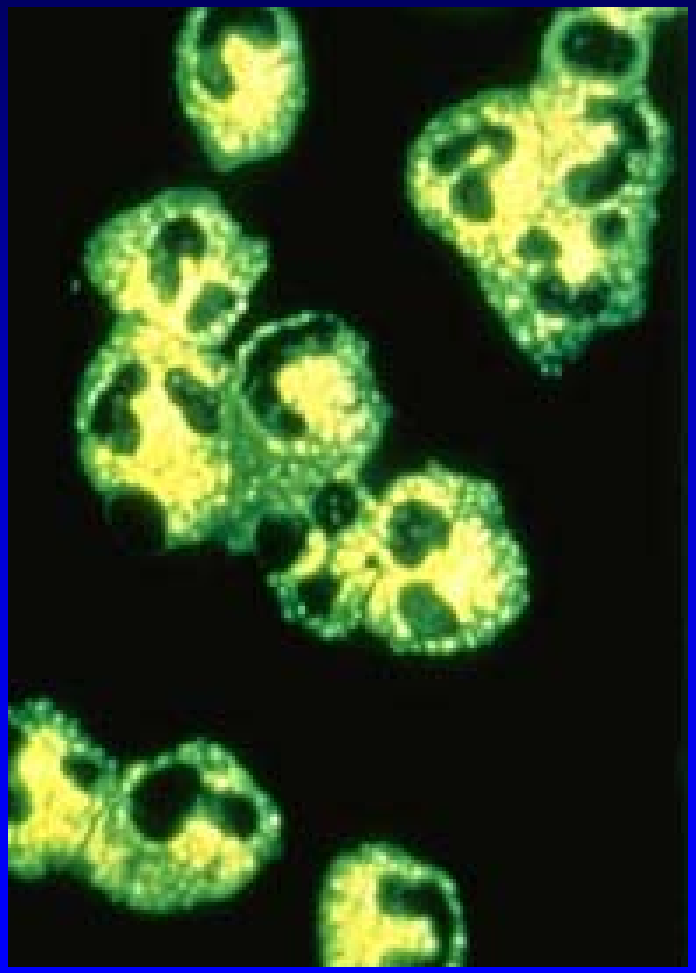
- sinus
- lung
- kidney

Multisystem disease

Can also affect:

- joint
- eye
- skin
- nerve
- other sites

Antineutrophil Cytoplasmic Antibodies (ANCA)



- 1982 Davies et al.

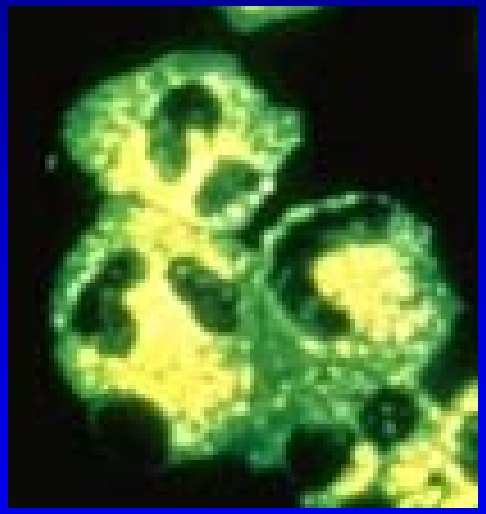
Detected serum IgG antibodies that stained neutrophil cytoplasm in 8 patients with segmental necrotizing glomerulonephritis

- 1985 Van der Woude et al.

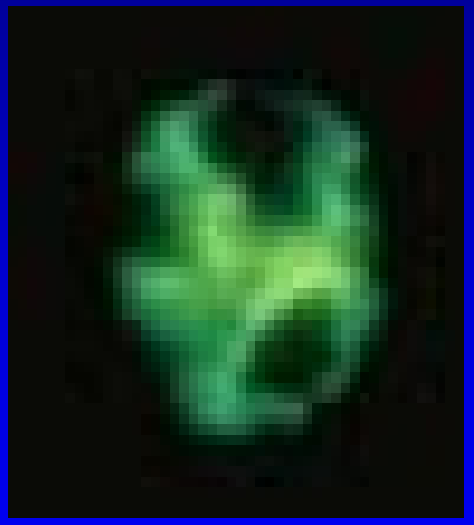
Demonstrated the association between cytoplasmic staining autoantibodies and active Wegener's granulomatosis

Antineutrophil Cytoplasmic Antibodies (ANCA)

cANCA
cytoplasmic staining



pANCA
perinuclear staining



Proteinase -3

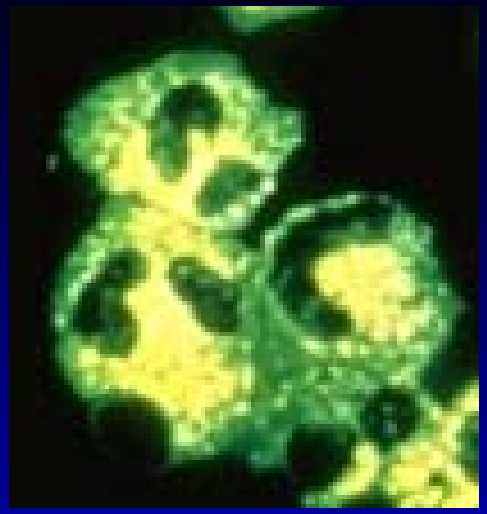
Target Antigens In Vasculitis

Myeloperoxidase

Methods of ANCA Testing

Indirect Immunofluorescence

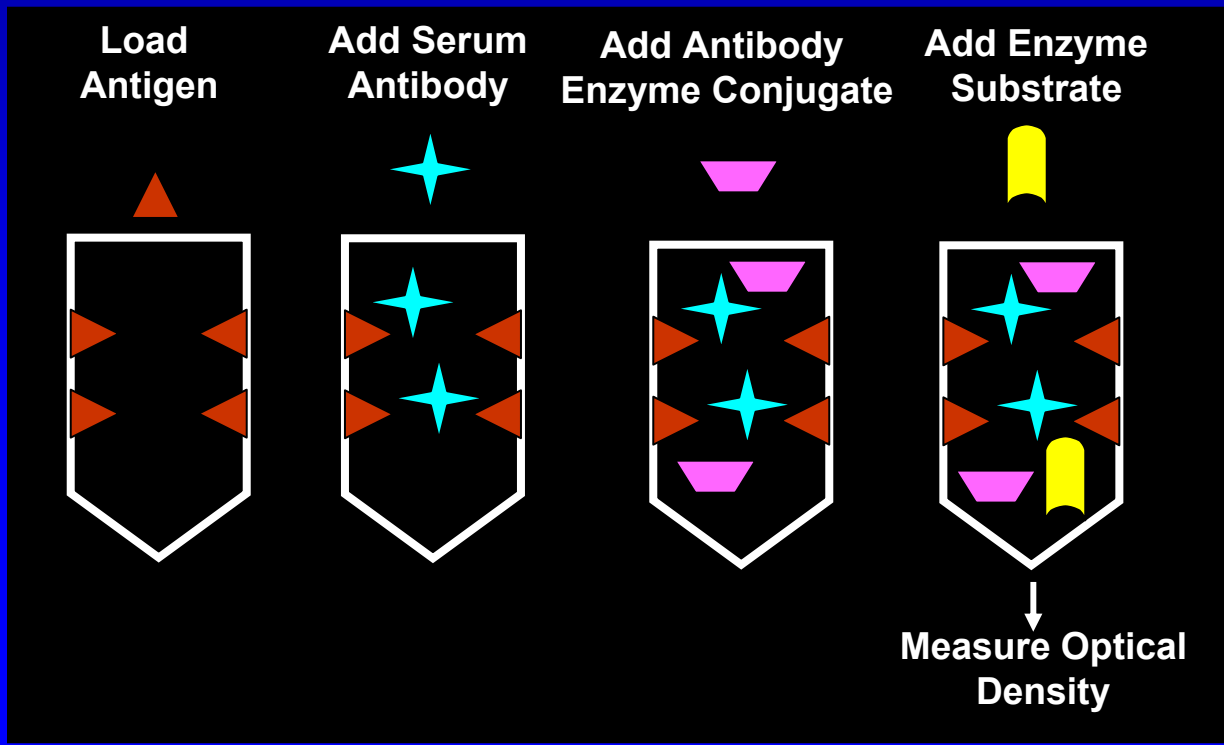
cANCA pANCA



ELISA

(target antigen-specific)

proteinase 3
myeloperoxidase

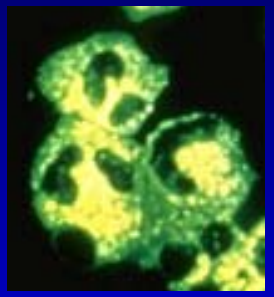


Wegener's granulomatosis (70-95%)
Microscopic polyangiitis (20-80%)
Churg-Strauss (5-20%)

} positive cANCA
positive anti-Pr 3 ELISA

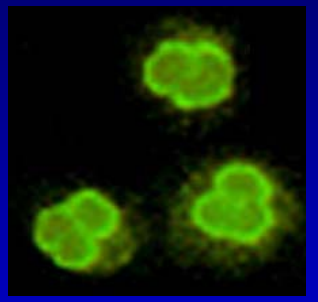
Case reports of associations

} positive cANCA
negative anti-Pr 3 ELISA



cANCA

A (+) cANCA or pANCA
should be confirmed
by antigen-specific (Pr 3, MPO) ELISA



pANCA

Wegener's granulomatosis (5-20%)
Microscopic polyangiitis (40-80%)
Churg-Strauss (20-70%)
Idiopathic crescentic glomerulonephritis

} positive pANCA
positive anti-MPO by ELISA

Inflammatory bowel disease
Other autoimmune diseases
Infection
Drugs

} positive pANCA
negative anti-MPO by ELISA

Key Issues Regarding ANCA

Clinical Applications

Can ANCA be used to diagnose Wegener's granulomatosis ?

Usually no – biopsy still required in most people

Do high ANCA levels indicate active vasculitis ?

Levels are higher overall in people with active disease but are not reliable in assessing disease activity in the individual patient

Pathophysiology

Are ANCA pathogenic or an epiphenomenon ?

Unclear

some *in vitro* and *in vivo* data support pathogenicity

there are also important contradictions in human disease

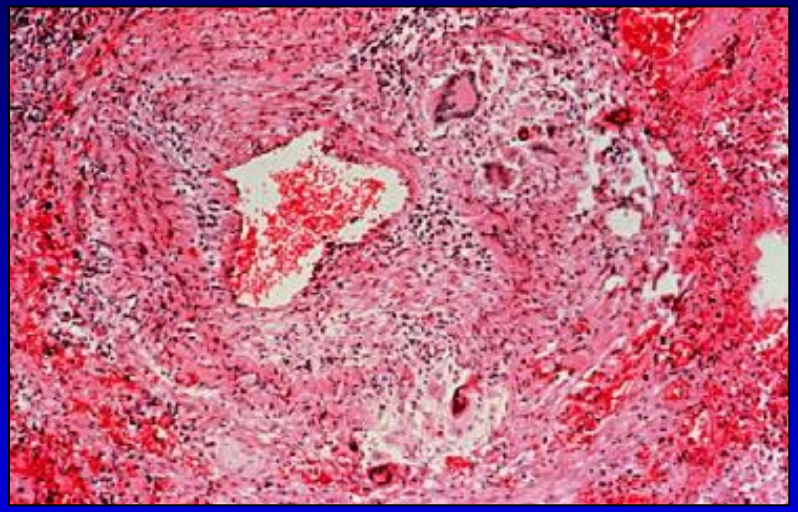
Wegener's Granulomatosis

Diagnosis

ANCA associated in 75-90% of patients

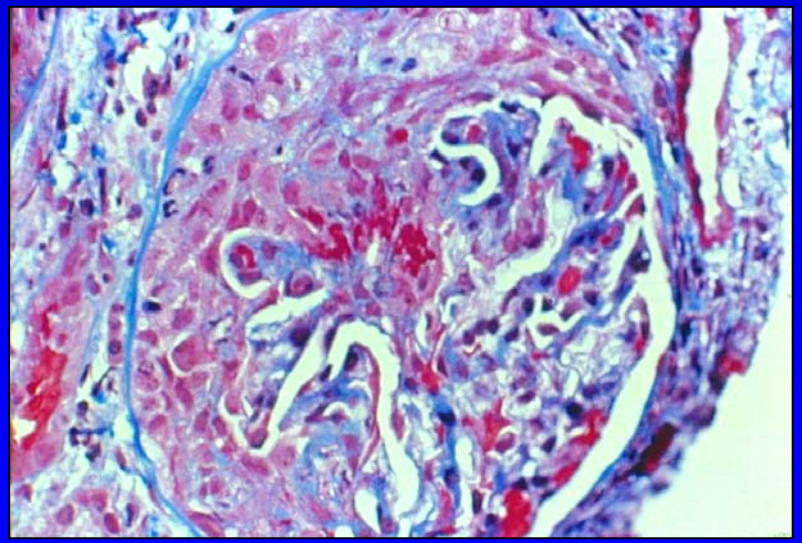
Sinus and Lung biopsies

- Necrosis
- Granulomatous inflammation
- Small vessel vasculitis



Kidney biopsy

- focal, segmental, crescentic, necrotizing GN
- few to no immune complexes
- (Pauci-immune Glomerulonephritis)



Wegener's Granulomatosis

Treatment Outcome

Prednisone + daily cyclophosphamide

Prednisone + methotrexate (for mild disease)

- Untreated disease – median survival time 5 months
  - Mortality from pulmonary or renal failure
- 80% survival with treatment
- Relapse occurs in 50%

Epidemiology

Microscopic Polyangiitis

Vasculitis of small vessels with few to no immune deposits
Frequently affects the glomerulus and pulmonary capillaries

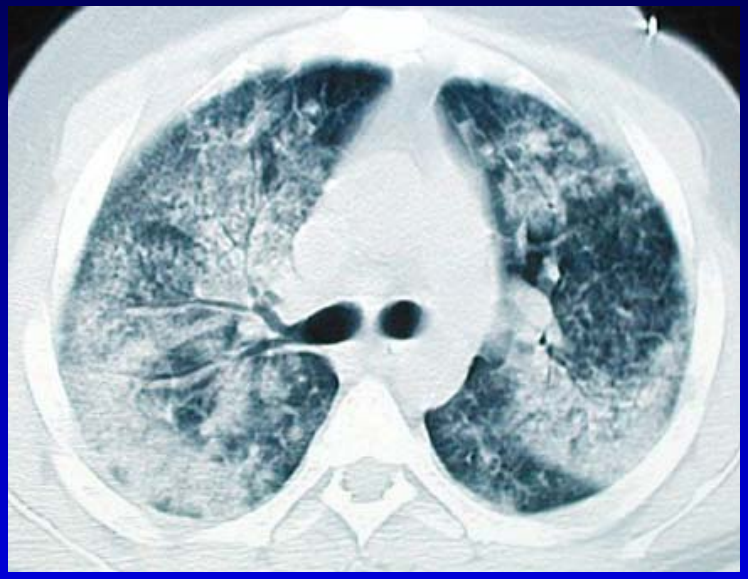
Separated from PAN in 1994

Has many similarities to Wegener's granulomatosis

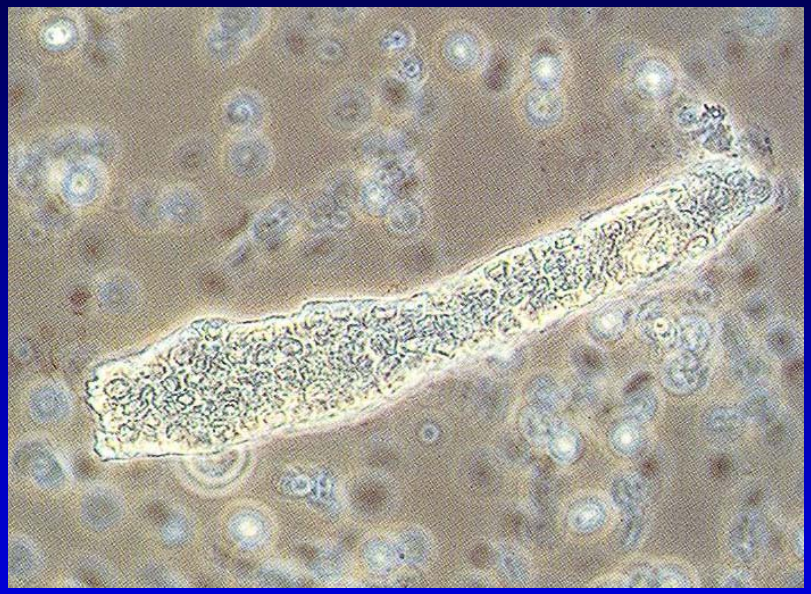
- small vessel disease
- ANCA-associated
- pulmonary hemorrhage and glomerulonephritis
- differs in lacking granulomatous inflammation

Microscopic Polyangiitis

Clinical Manifestations



pulmonary – alveolar hemorrhage



renal – glomerulonephritis

Other prominent sites of involvement
nerve
skin

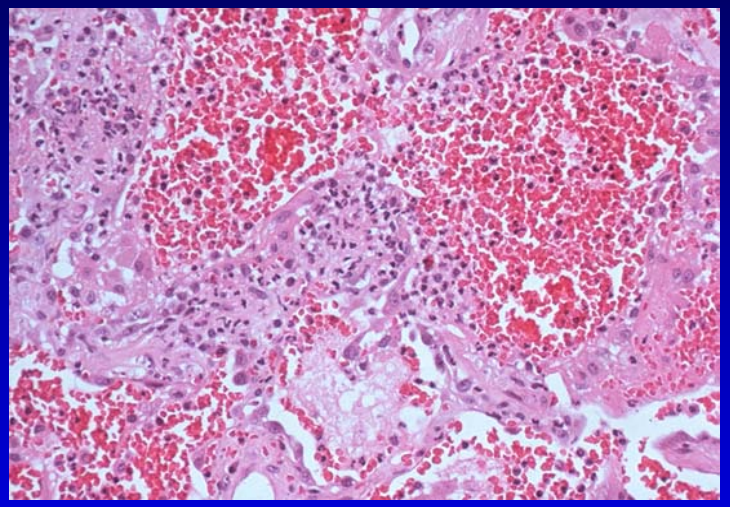
Diagnosis

Microscopic Polyangiitis

pANCA (anti-MPO) - found in 50-80% of patients

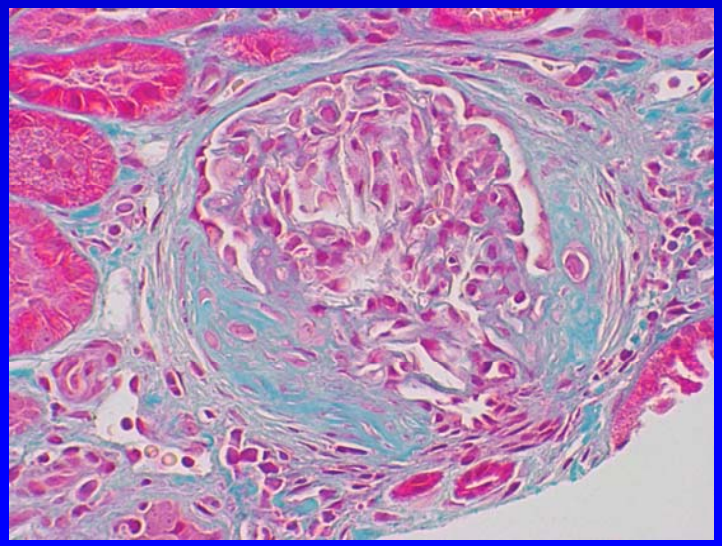
Can suggest MPA

Should generally not be used for diagnosis



Lung biopsies

Small vessel vasculitis



Kidney biopsy

focal, segmental, crescentic, necrotizing GN

few to no immune complexes

(Pauci-immune Glomerulonephritis)

Microscopic Polyangiitis

Treatment Outcome

Prednisone + daily cyclophosphamide

Prednisone + methotrexate (for mild disease)

- 74% estimated 5 year survival
- Relapses occur in at least 34%

Churg-Strauss Syndrome

Epidemiology

Vasculitis of small to medium-sized vessels

Eosinophilic and granulomatous inflammation of the respiratory tract

Uncommon – affects 3 people per million

Men = Women

Churg-Strauss Syndrome

Clinical Manifestations

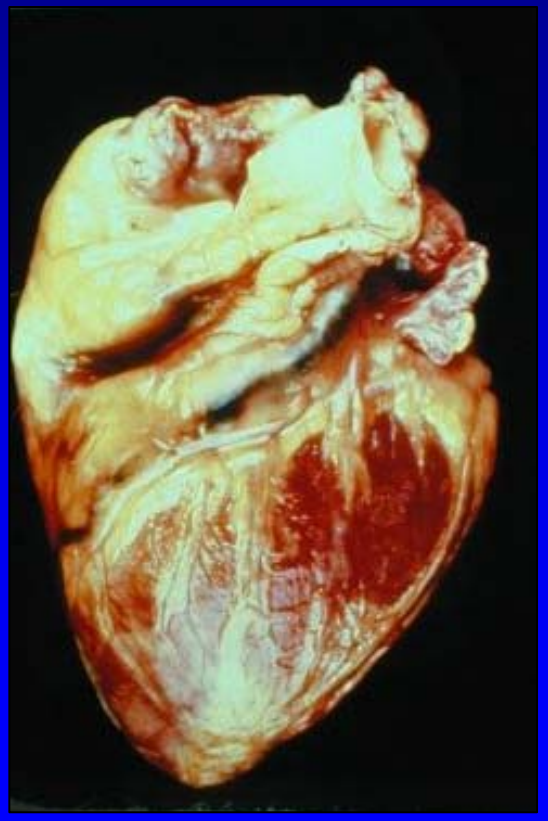
Thought of as having 3 phases

(Helpful conceptually but - not seen in all patients
often do not occur in sequence)

Prodromal phase: asthma, allergic rhinitis

Eosinophilic phase: peripheral eosinophilia
eosinophilic tissue infiltrates

Vasculitic phase: nerve
skin
lung
GI tract
heart



From the ACR Slide Collection

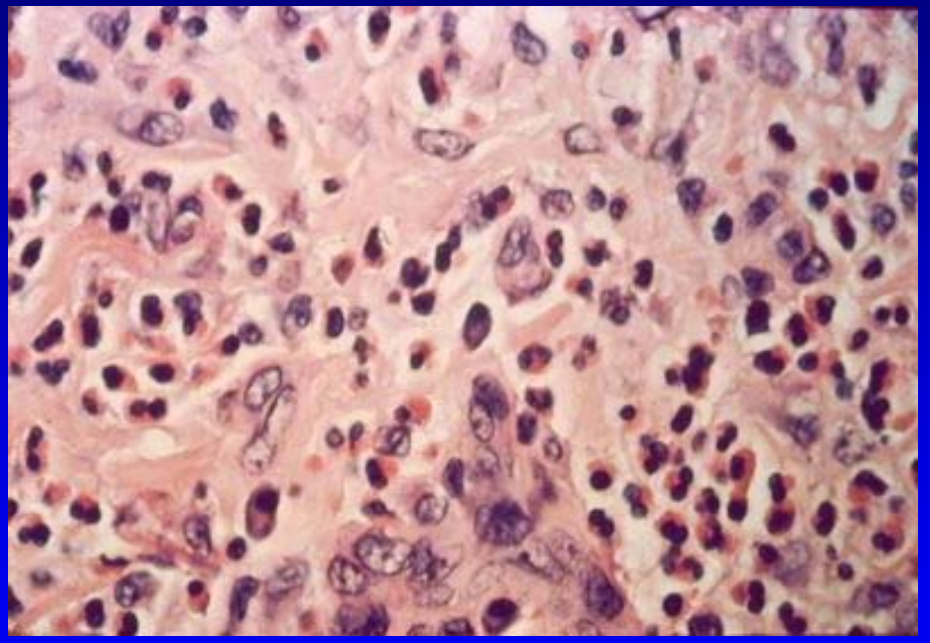
Churg-Strauss Syndrome

Diagnosis

ANCA associated in 2-50% of patients

Biopsy:

eosinophilic tissue infiltrates
extravascular “allergic granuloma”
small vessel vasculitis



Often difficult to demonstrate

Diagnosis often based on clinical features:
asthma, hypereosinophilia, clinical manifestations consistent with vasculitis

Churg-Strauss Syndrome

Treatment Outcome

Prednisone

Severe disease: prednisone + daily cyclophosphamide

- Prognosis influenced by factors of severe disease (GI, renal, cardiac, CNS)

Cardiac involvement main cause of patient mortality

- Vasculitic relapses occur in 26%
- Relapses of asthma are frequent and may limit ability to taper prednisone

Henoch-Schönlein Purpura

Epidemiology

Small vessel vasculitis
Immune complex - IgA deposits

Affects predominantly children
75% occur before the age of 8 years

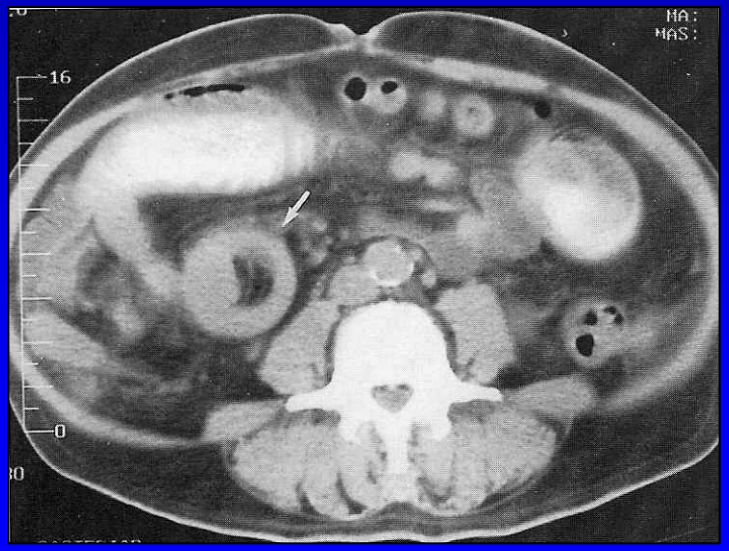
2/3 of patients report an antecedent respiratory infection

Henoch-Schönlein Purpura

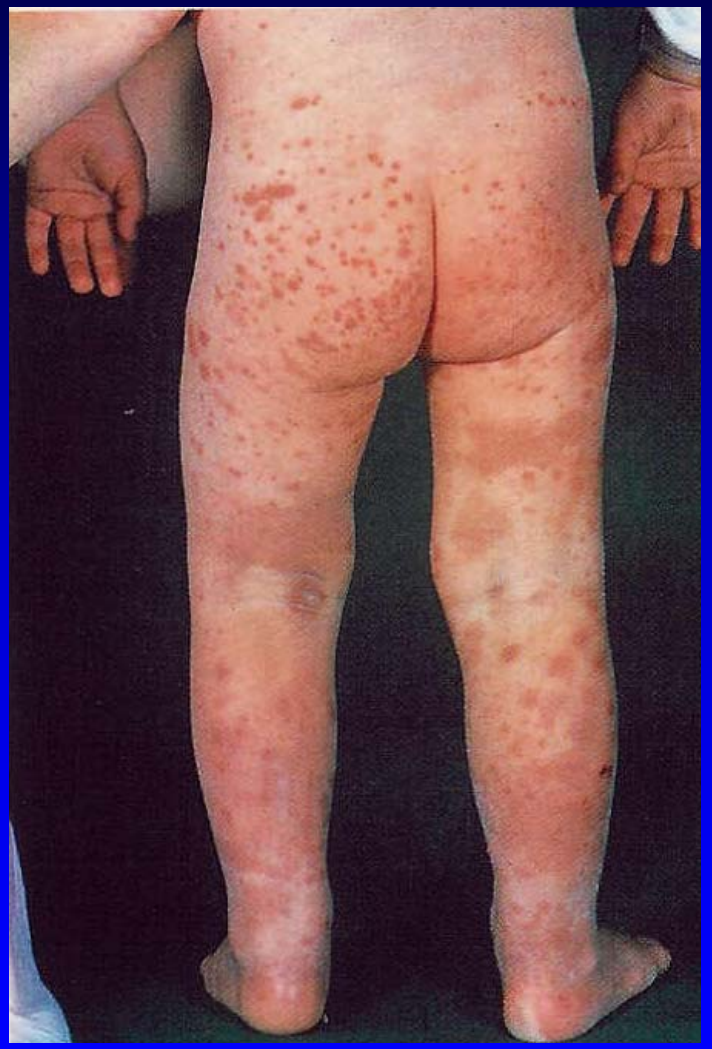
Clinical Manifestations

4 cardinal manifestations:

- palpable purpura
- arthritis
- glomerulonephritis
- GI involvement (intussception)



From: Davis. Fundamentals of Gastrointestinal Radiology



From Klippel and Dieppe. Rheumatology

Henoch-Schönlein Purpura

Diagnosis

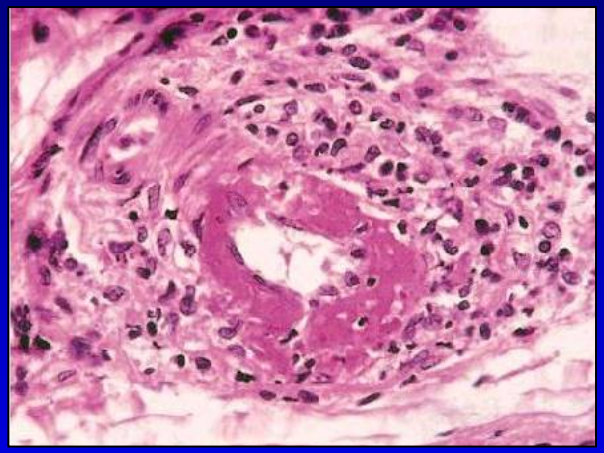
Diagnosis established by the pattern of clinical manifestations

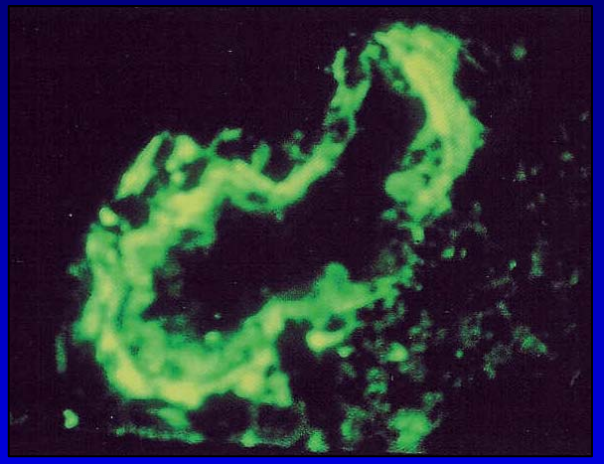
Biopsies (usually not required)

Skin

Leukocytoclastic
small vessel vasculitis

(+) IgA deposits

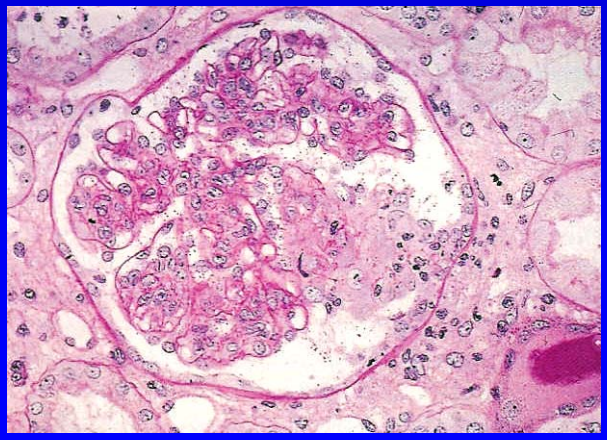


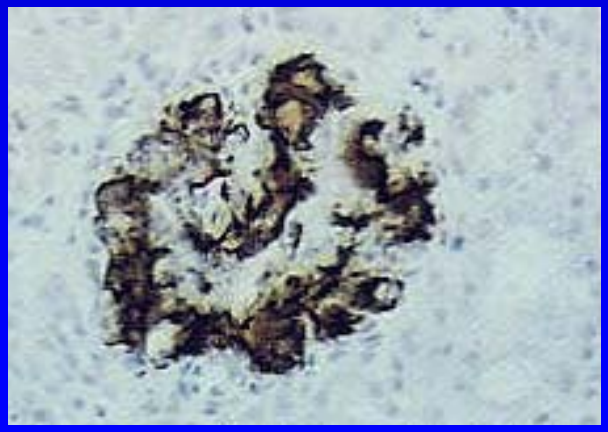


Kidney

Mesangial proliferation
Segmental, crescentic
glomerulonephritis

(+) IgA often IgG and C3
May have prognostic utility





From: Churg and Churg. Systemic Vasculitis

Henoch-Schönlein Purpura

Treatment Outcome

Treatment rarely required - typically self-limited

Prednisone

may reduce arthritis, abdominal discomfort, risk of intussusception

Prednisone + cytotoxic therapy

consider for active glomerulonephritis with renal function loss

- 1-3% disease related mortality
- Relapses occur in 40%, usually within first 3 months
- ESRD – 2-5% in children, may be up to 13% in adults
- adults may have more severe disease

Cryoglobulinemic Vasculitis

Epidemiology

Small vessel vasculitis with cryoglobulin immune deposits

Cryoglobulin – cold-precipitable monoclonal or polyclonal immunoglobulin

Can occur in conjunction with a variety of disease processes

- Plasma cell or lymphoid neoplasms (myeloma)
- Chronic infection
- Connective tissue diseases

Majority of cases of cryoglobulinemic vasculitis related to HCV

Cryoglobulinemic Vasculitis

Clinical Manifestations

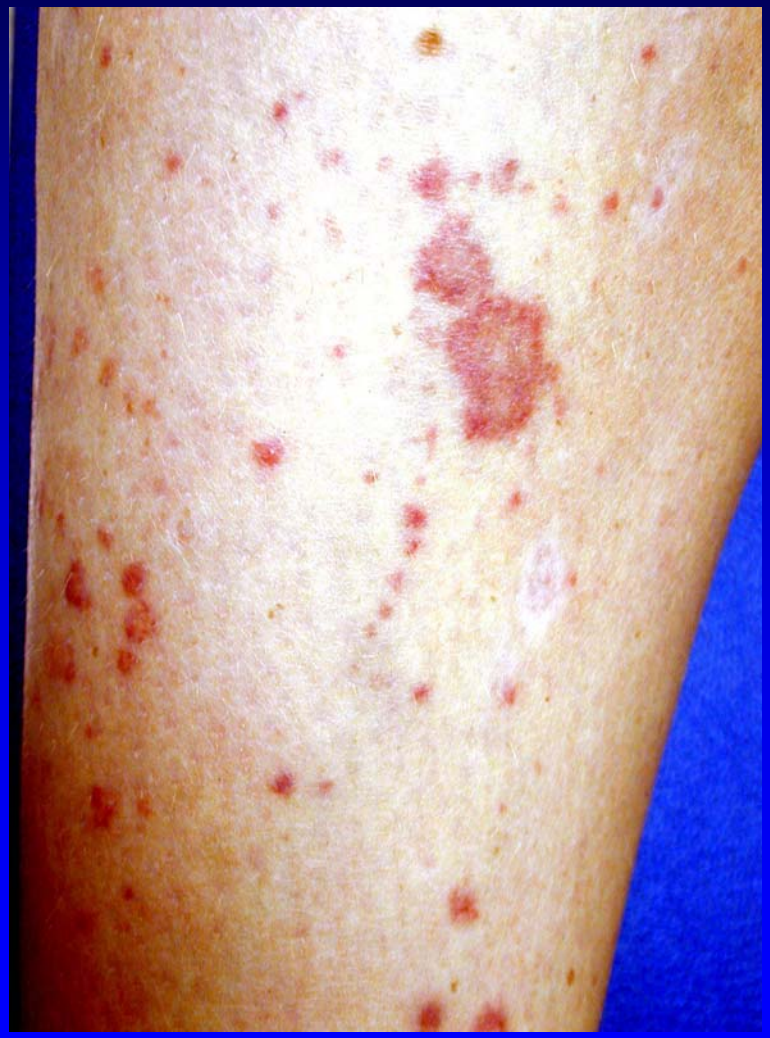
Palpable purpura

Arthritis

Neuropathy

Glomerulonephritis

- occurs in 10-50%
- proteinuria, hematuria
- rarely rapidly progressive



Cryoglobulinemic Vasculitis

Diagnosis

Diagnosis is usually clinical combining:

- compatible clinical findings
- laboratory features supportive of cryoglobulinemia
- when possible an underlying cause

Laboratories:

(+) cryoglobulins - are difficult to measure
(+) rheumatoid factor
(+) hepatitis C (if negative search for other causes)
Hypocomplementemia

Biopsies

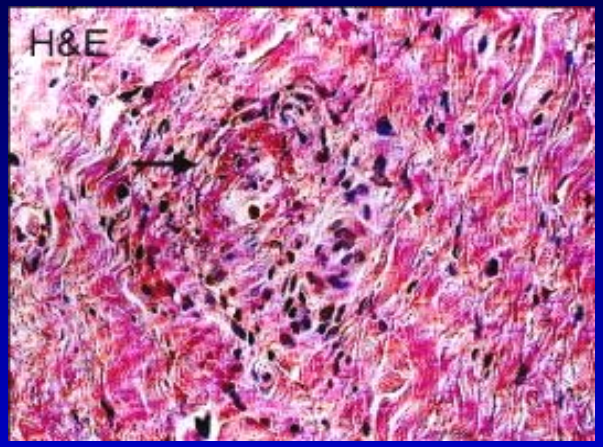
May be useful in selected settings

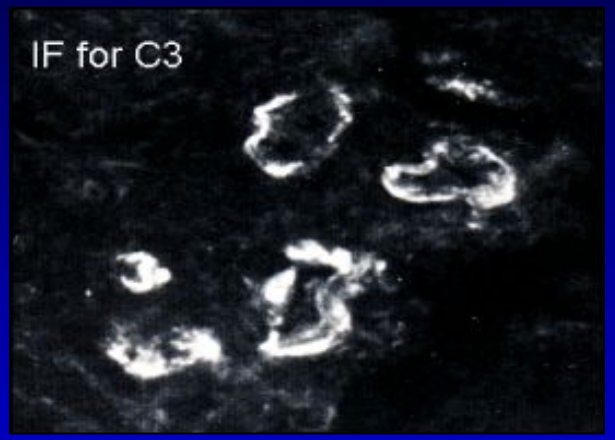
Cryoglobulinemic Vasculitis

Diagnosis

Biopsies

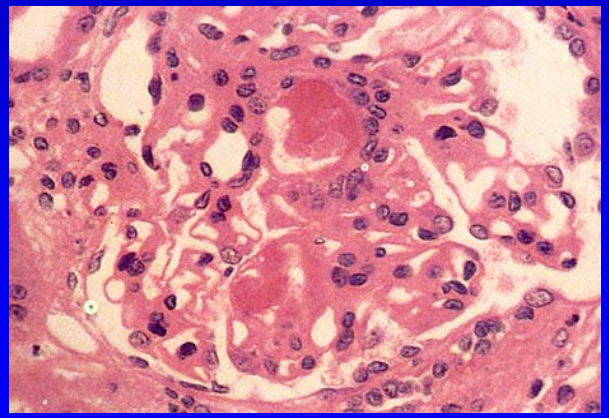
Skin

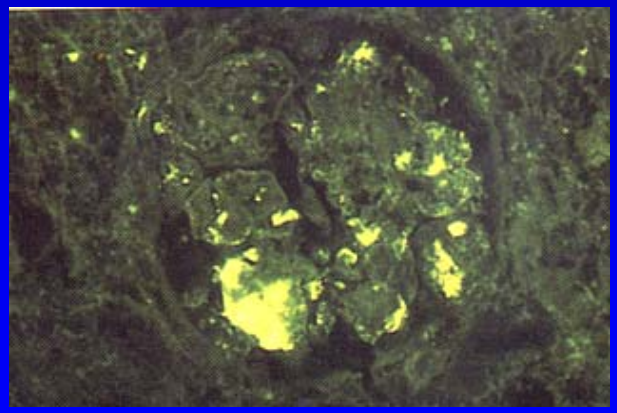




From: Churg and Churg. Systemic Vasculitis

Kidney





From: Kern et al. Atlas of Renal Pathology

Membranoproliferative glomerulonephritis
Acellular intraluminal protein (cryoglobulins), (+) immunofluorescence

Cryoglobulinemic Vasculitis

Treatment Outcome

Treat underlying process

Hepatitis C-associated – peginterferon + ribavirin

Immunosuppressive therapy

anecdotal experience only – may increase hepatitis C viremia

Plasmapheresis

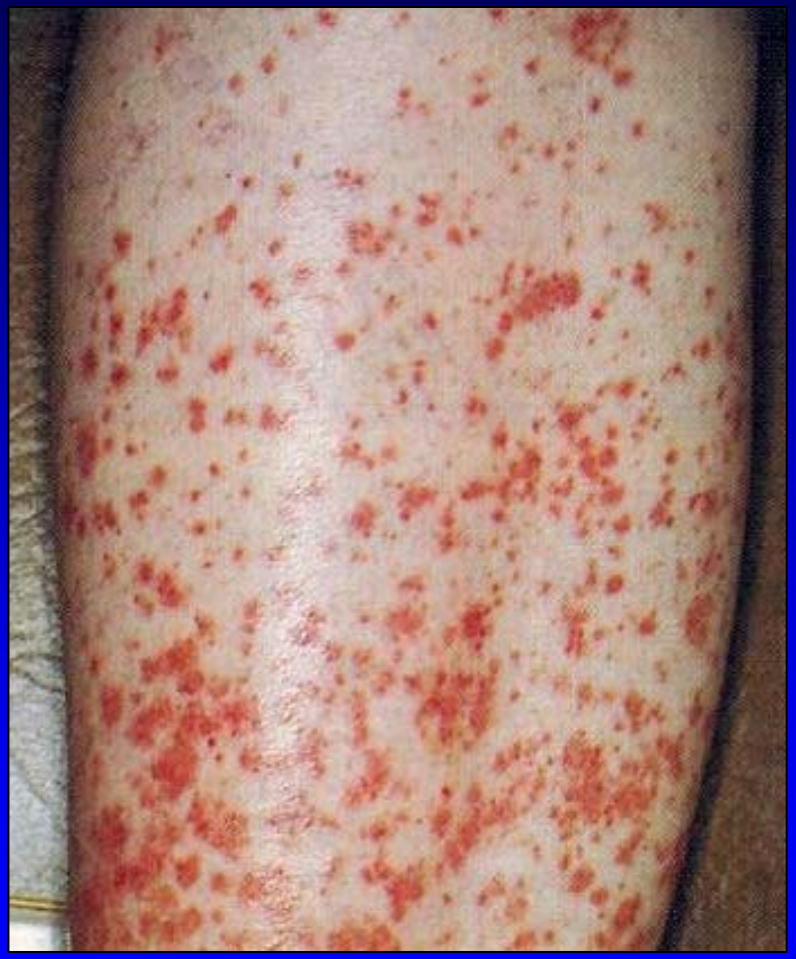
brief responses but not a long-term option

For HCV-associated cryoglobulinemic vasculitis:

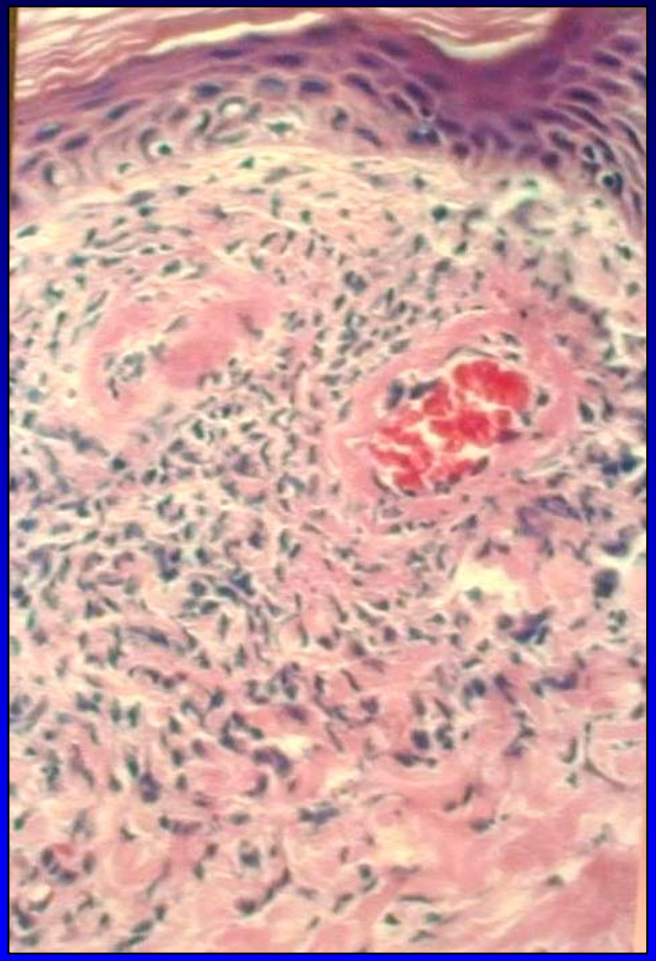
- improvement in vasculitis is associated with clearance of viremia
- Relapse typically occurs with return of viremia

Cutaneous Leukocytoclastic Vasculitis

Small vessel vasculitis of the skin - most commonly encountered vasculitis



Manifests clinically: palpable purpura



Leukocytoclasis: nuclear disruption

From: Klippel and Dieppe. Rheumatology

Cutaneous Leukocytoclastic Vasculitis

> 70% occur in the setting of an underlying process:

- medication
- infection
- malignancy
- connective tissue disease
- heralding feature of a primary systemic vasculitis

When no cause found: idiopathic cutaneous vasculitis

Treatment:

Treat/remove underlying disease/exposure when present

Idiopathic: use least toxic yet effective regimen

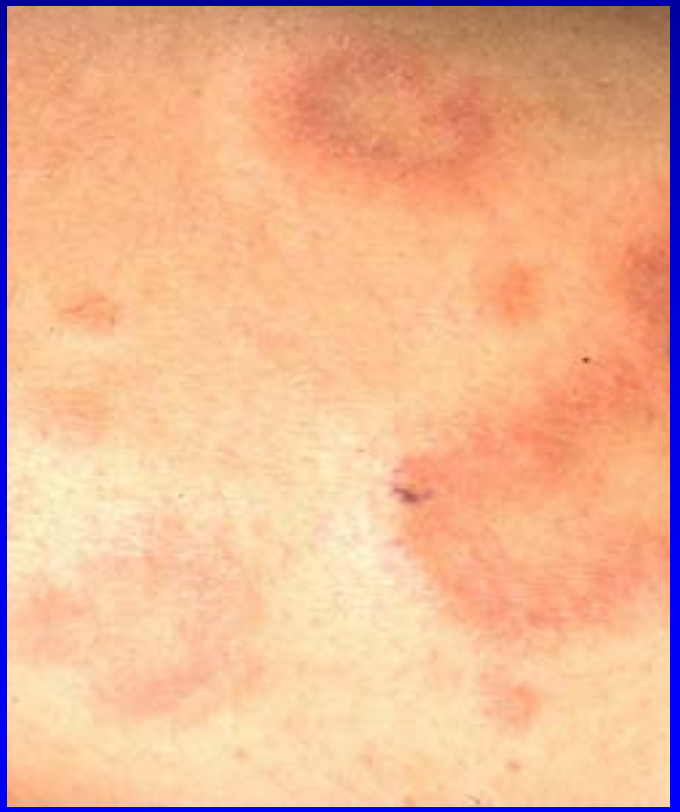
Urticarial Vasculitis

Consists of two key elements:

- Clinical manifestations of urticaria
- Histology: leukocytoclastic vasculitis, largely involving postcapillary venules

Skin lesions differ from common urticaria:

- Wheals may have a central dark or red appearance
- Lesions last > 24 hours
- Often resolve with residual hyperpigmentation
- Typically painful with a burning/stinging sensation
- Pruritis less common than true urticaria

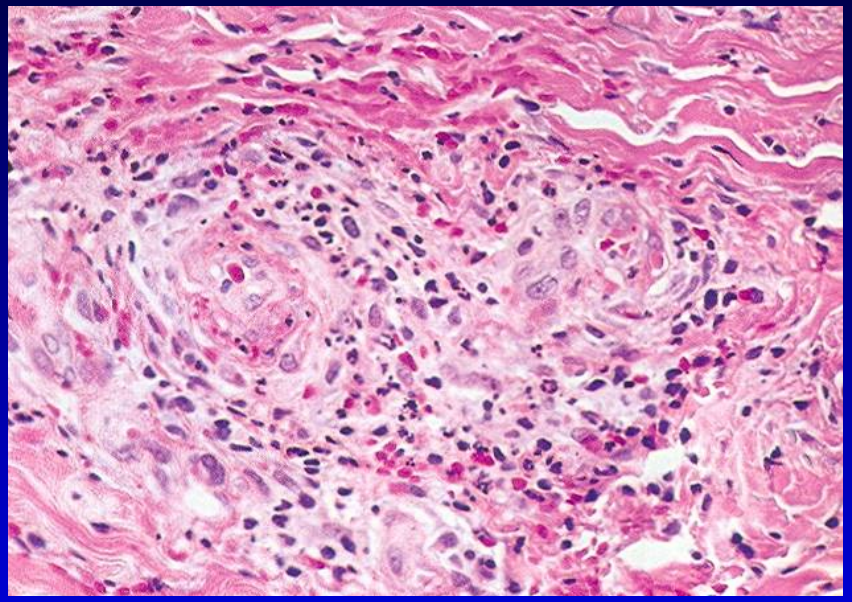


Can be associated with systemic features

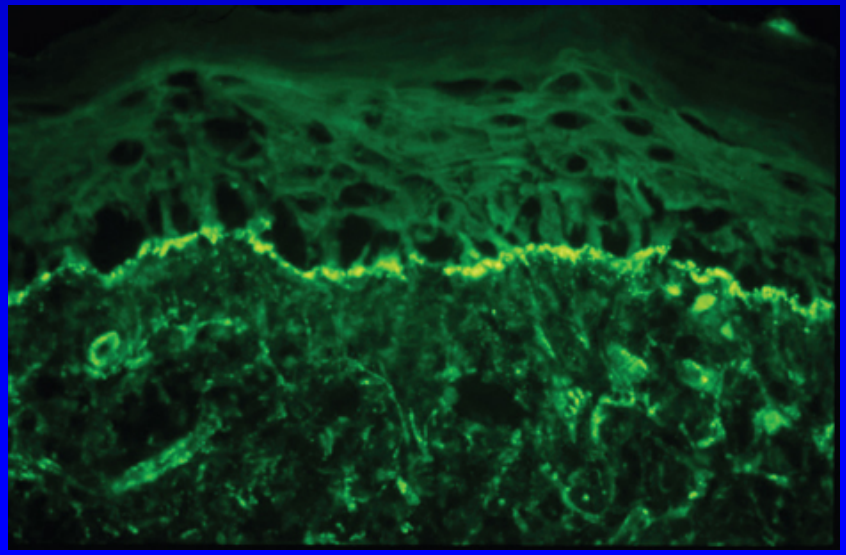
- Musculoskeletal (arthralgias, arthritis)
- Pulmonary (COPD)
- Renal
- GI

Urticarial Vasculitis
Histology

Leukocytoclastic vasculitis



~80% will have (+) immunofluorescence: immunoglobulin, complement or fibrin
- around blood vessels
- basement membrane zone of dermal-epidermal junction



Not specific for urticarial vasculitis and can be seen in SLE

Urticarial Vasculitis

Normocomplementemic urticarial vasculitis (NUV)

Most cases are idiopathic

Can be secondary to:

- Monoclonal gammopathy
- Neoplasia
- Ultraviolet light sensitivity
- Repeated cold exposure

Hypocomplementemic urticarial vasculitis (HUV)

Most are secondary to:

- Systemic lupus erythematosus
- Sjögren's syndrome
- Serum sickness reaction
- Neoplasia

HUVS

Complement – CH50, C3, C4, C1q

To conclusively state as normal - values should be repeated on 2-3 occasions over several months of observation during both activity and quiescence

Urticarial Vasculitis
Laboratory Studies and Investigations

Obtain in patients with a compatible clinical and histologic picture to detect hypocomplementemia and systemic features:

- Complement (CH50, C3, C4, C1q)
- CBC with differential
- Urinalysis
- Chemistries
- Hepatitis B and C serologies
- ANA, anti-DNA, ENA
- ANCA
- RF and anti-CCP
- SPEP
- Cryoglobulins

Consider other investigations as appropriate:

- chest imaging
- Skeletal radiographs in patients with joint pain
- PFTs (to look for COPD)

Urticarial Vasculitis

Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS)

Specific autoimmune disorder that involves > 6 months of urticaria with hypocomplementenia in the presence of systemic findings

Clinical features

- Urticarial vasculitis is the dominant feature
- Angioedema occurs in 50% and can be the presenting feature
- Moderate to severe COPD occurs in 50%
- Ocular inflammation (uveitis) occurs in 30%
- Can get glomerulonephritis
- Many features resemble SLE (some propose it is a subset of SLE)

Labs

- C3, C4 can be undetectable to low normal
- C1q low in all patients when disease is active
- Anti-C1q antibodies (C1q precipitins) detectable in all patients
- Anti-DNA and anti-Sm are uncommon

Urticarial Vasculitis

Hypocomplementemic Urticarial Vasculitis Syndrome (HUVS)

Diagnostic criteria *(Schwartz et al. Mayo Clin Proc 1982;57:231)*

Major criteria (both must be present)

- Urticaria for more than 6 months
- Hypocomplementemia

Minor criteria (must have 2 or more)

- Venulitis of the dermis (established via biopsy)
- Arthralgia or arthritis
- Mild glomerulonephritis
- Uveitis or episcleritis
- Recurrent abdominal pain
- Positive C1q precipitin test with an associated suppressed C1q level

Urticarial Vasculitis
Treatment

Treat underlying disease if one is present

For cutaneous lesions, variable efficacy:

- Prednisone
- Hydroxychoroquine
- Dapsone
- Colchicine

For severe systemic disease:

- Systemic immunosuppression may be required

For HUVS

- Treatment as above for cutaneous or systemic disease
- Some series have shown stabilization with cyclosporin
- COPD often presents significant challenges

Vasculitis - Conclusion

Goal Highlight important aspects of vasculitic disease that may appear on Allergy Board exams or in Allergy clinical practice

Recognize This summary is not all encompassing:

- Other rare forms of vasculitis
- The vasculitides are complex diseases

For more information on vasculitis:

Concise references:

Primer on Allergic and Immunologic Diseases

Harrison's Textbook of Internal Medicine

Detailed references:

Ball & Bridges. Vasculitis. 2002

Hoffman & Weyand. Inflammatory Diseases of Blood Vessels. 2002

Questions regarding a vasculitis patient

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